IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant:	Joseph ROBERTS, *et al.*
Title:	PEGYLATION OF THERAPEUTIC AGENTS
Appl. No.:	09/972,245
Filing Date:	10/09/2001
Examiner:	Richard A. Schnizer
Art Unit:	1635
Confirmation No.:	3976

BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
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Sir:

Under the provisions of 37 C.F.R. § 41.37, this Appeal Brief is being filed together with a credit card payment form in the amount of $250.00 covering the 37 C.F.R. 41.20(b)(2) appeal fee for a small entity. If this fee is deemed to be insufficient, authorization is hereby given to charge any deficiency (or credit any balance) to the undersigned deposit account 19-0741.

REAL PARTY IN INTEREST

The named inventors of the above-captioned application have assigned all rights, title, and interest in the invention to the University of South Carolina.

RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any appeals or interferences that will directly affect or be directly affected by or have a bearing on the Board's decision in the present appeal.

STATUS OF CLAIMS

1. Claims pending: 1-46
2. Claims rejected: 1-13, 17-22, and 41-46
3. Claims on appeal: 1-13, 17-22, and 41-46
4. Claims withdrawn: 14-16 and 23-40

A copy of claims 1-13, 17-22 and 41-46 is provided in the Claims Appendix. All of these claims have been finally rejected.

STATUS OF AMENDMENTS

In the Final Office Action dated December 29, 2005, the PTO entered and considered all of the amendments set forth in the Amendment and Reply Under 37 C.F.R. §1.111 that was filed on October 6, 2005. No amendments were submitted after the Final Office Action of December 29, 2005.

SUMMARY OF CLAIMED SUBJECT MATTER

The presently claimed invention relates to a method for determining the modification conditions that protect therapeutic compositions from host-mediated inactivation. See Specification, page 1, lines 3-4.

The Examiner has confused measuring an immune response to the introduction of a biological agent with measuring the extent of remaining functional activity of a biological agent following introduction of that biological agent into a host.

When a host encounters a foreign agent in its circulation, the host's immune system may initiate an immune response. This response includes the production of agent-inactivating antibodies that also enable the reticuloendothelial system to clear the agent from circulation. Thus, the therapeutic life of an administered non-human agent is often limited by the host's immune system. Furthermore, the problem of host-mediated defense limits the usefulness of

human proteins that either are not generally found in circulation or are produced in heterologous systems, using recombinant DNA technology (Nucci, ML, Short, R and Abuchowski, A., 1991. Advanced Drug Delivery Reviews, 6:133-151). See Specification, page 1, lines 7-14.

Before Applicants work, various methods looked at biological response to an agent in a treated subject, namely immunogenicity which is assumed to correlate with the loss of functional activity or antigenicity which compares the extent of shielding of the compound by the modifying agent to biological response to the unmodified agent. In these methods, however, functional activity of the biological agent was in fact determined before administration in order to determine the loss of acceptable activity which, to the most part, determined the extent to which a compound can be modified. This is very different, however, from the functional activity recovered after the administration of the modified biological agent to a subject as described by Applicants in the present application.

The existing criteria (antigenicity, immunogenicity and acceptable loss of bioactivity) for determining the activated PEG used and the extent of PEGylation are insufficient for ascertaining the modification for an agent in instances where such agents are administered to a patient over a prolonged period of time. This is true, because none of the foregoing criteria take into consideration the effect of the host's response on the agent's biological activity after the PEGylated agent is administered to the host. As a result, reliance on only the aforementioned criteria will produce an agent that is not optimally protected from the host's immune system, or otherwise from *in situ* inactivation. See Specification, page 2, lines 16-23.

Accordingly, there is a great and present need for a strategy that would enable the skilled artisan to determine the extent of PEGylation for a given agent that is administered to a patient during prolonged periods of therapy. The inventors have found that when a novel, physiologically relevant optimization scheme is applied and the modifying agent is a polyethylene glycol, these modification ("PEGylation") ranges are not commensurate with the highest suitable PEGylation range as determined by employing an *in vitro* assay that monitors loss of therapeutic activity, antigenicity and immunogenicity. Currently, these *in vitro* methods of determining suitable PEGylation ranges are the only existing method as described in the art. The inventors' discovery suggests that over-PEGylation of an agent, as well as

over-modification of an agent with any modifying agent, can disrupt the secondary and/or tertiary structure of the agent, thus exposing new antigenic determinants to the immune system. It is understood that this observation applies equally to other bio-compatible polymers or agents used to increase the useful circulating half-life of therapeutic agents. See Specification, page 2, line 24 – page 3, line 8.

The methods as provided in the current invention involve ascertaining the modification conditions of a therapeutic agent, by assessing the biological activity of the modified agent, after administration to an animal or subject. By "biological activity" is meant a cellular or physiological response or reaction that that agent causes, either directly or indirectly. The biological activity can be assessed *in vivo*, *in vitro* or *in situ*. Examples of biological activity include, but are not limited to, an enzyme catalyzing a reaction, a molecule binding a receptor or antibody, mediating a receptor-mediated response such as ion influx/efflux or generation of second messengers, antagonizing or blocking a receptor-mediated response, induction of apoptosis and release or uptake of a neurotransmitter or hormone. The biological activity is not necessarily the same activity as the therapeutic benefit that the agent bestows upon the subject. For example, a skilled artisan could measure the ability of a modified therapeutic to bind to a receptor, *in vitro* or *in situ*, to demonstrate that the therapeutic agent confers a therapeutic benefit. However, the type of assay to be employed will vary, according to the type of therapeutic that is being administered. A suitable assay is any assay that is able to detect the biological activity of the therapeutic. For example, if the administered agent possesses glutaminase activity, then a suitable assay in this instance would be one that is able to detect any such glutaminase activity (Roberts, J., 1976. Journal ofBiological Chemistry, 251:2119-2123). If the administered therapeutic is a vector which comprises a nucleic acid sequence, for example, capable of transcribing a polypeptide that possesses a biological activity, then a suitable assay would be an assay capable of detecting the biological activity of the transcribed polypeptide. If the administered therapeutic does not have a simple assay to measure biological activity in the serum, immunological assays can be used to quantify the amount of the therapeutic composition in the serum. See Specification, page 13, lines 4-26.

The presently claimed invention is a method to determine the optimal modification of a biological agent so that it retains its functional activity during the course of therapy, which

might involve repeated administration. To be able to do that, the present inventors developed a method which determines if the biological agent retains its functional activity during the course of therapy. The present inventors accomplished this by measuring the functional activity of a therapeutic agent after the first and subsequent administration from a sample obtained from the treated subject to thereby determine the extent of modification that best reserves the functional activity after repeated administration.

The presently claimed invention provides a method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of the therapeutic agent when covalently modified by the biocompatible polymer. The method includes the steps of:

(a) assaying a biological activity of a first modified therapeutic agent after the first modified therapeutic agent has been administered to a subject, wherein the first modified therapeutic agent is covalently modified with a biocompatible polymer;

(b) assaying the biological activity of the first modified therapeutic agent after at least one booster dose of the first modified therapeutic agent has been administered to the subject;

(c) assaying the biological activity of a second modified therapeutic agent after the second modified therapeutic agent has been administered to a subject, wherein the second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of the first modified therapeutic agent;

(d) assaying the biological activity of the second modified therapeutic agent after at least one booster dose of the second modified therapeutic agent has been administered to the subject; and

(e) comparing the biological activity of the first modified therapeutic agent with the biological activity of the second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of the therapeutic agent when covalently modified by the biocompatible polymer. See Specification, page 21, line 7-page 24, line 2.

The reference to "the biological activity" in each of steps (b), (c), (d), and (e) refers to the *same* biological activity recited in step (a).

According to a preferred embodiment of this claimed method, the biocompatible polymer may be a polyethylene glycol ("PEG") which is selected from the group consisting of mono-methoxy succinimidyl butanoate (SBA)-PEG, succinimidyl carbonate (SC)-PEG, aldehyde (ALD)-PEG, and succinimidyl propionate (SPA)-PEG. See Specification, page 15, lines 12-20.

According to another preferred embodiment of this claimed method, the therapeutic agent may be a polypeptide which is used to treat viral infections in patients in need of treatment thereof. See Specification, page 8, lines 23-27.

According to another preferred embodiment of this claimed method, the therapeutic agent may be a polypeptide which is used to lower glutamine levels in a subject. See Specification, page 10, line 17-page 12, line 2.

According to another preferred embodiment of this claimed method, the therapeutic agent may be a pharmaceutical composition which includes an excipient. According to a variant of this preferred embodiment, the excipient protects the therapeutic agent during lyophilization. See Specification, page 18, lines 15-21.

According to another preferred embodiment, the therapeutic agent comprises glutaminase-asparaginase. See Specification, page 10, line 17-page 12, line 2.

According to yet another preferred embodiment, therapeutic agent comprises *Pseudomonas* glutaminase-asparaginase. According to a variant of this embodiment, *Pseudomonas* glutaminase-asparaginase is modified with polyethylene glycol. See Specification, page 10, line 17-page 12, line 2.

Another aspect of the presently claimed invention provides a method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of the therapeutic agent when covalently modified by the biocompatible polymer. The method includes the following steps:

(a) selecting a biological activity;

(b) assaying the selected biological activity of step (a) of a first modified therapeutic agent after the first modified therapeutic agent has been administered to a subject,

wherein the first modified therapeutic agent is covalently modified with a biocompatible polymer;

(c) assaying the selected biological activity of step (a) of the first modified therapeutic agent after at least one booster dose of the first modified therapeutic agent has been administered to the subject;

(d) assaying the selected biological activity of step (a) of a second modified therapeutic agent after the second modified therapeutic agent has been administered to a subject, wherein the second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of the first modified therapeutic agent;

(e) assaying the selected biological activity of step (a) of the second modified therapeutic agent after at least one booster dose of the second modified therapeutic agent has been administered to the subject; and

(f) comparing the selected biological activity of step (a) of the first modified therapeutic agent with the selected biological activity of step (a) of the second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of the therapeutic agent when covalently modified by the biocompatible polymer. See Specification, page 21, line 7-page 24, line 2.

Again, the reference to "the biological activity" in each of steps (b), (c), (d), (e), and (f) refers to the *same* biological activity recited in step (a).

Yet another aspect of the presently claimed invention provides a method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of the therapeutic agent when covalently modified by the biocompatible polymer. The method includes the following steps:

(a) selecting a biological activity;

(b) assaying the selected biological activity of step (a) of a first modified therapeutic agent after the first modified therapeutic agent has been administered to a subject,

wherein the first modified therapeutic agent is covalently modified with a biocompatible polymer;

(c) assaying the selected biological activity of step (a) of the first modified therapeutic agent after at least one booster dose of the first modified therapeutic agent has been administered to the subject;

(d) assaying the selected biological activity of step (a) of a second modified therapeutic agent after the second modified therapeutic agent has been administered to a subject, wherein the second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of the first modified therapeutic agent;

(e) assaying the selected biological activity of step (a) of the second modified therapeutic agent after at least one booster dose of the second modified therapeutic agent has been administered to the subject; and

(f) comparing the selected biological activity of step (a) of the first modified therapeutic agent with the selected biological activity of step (a) of the second modified therapeutic agent to determine the relative bioavailability of the first modified therapeutic agent and the second therapeutic agent (g) selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of the therapeutic agent when covalently modified by the biocompatible polymer based upon the comparison of step (f). See Specification, page 21, line 7-page 24, line 2.

The reference to "the biological activity" in each of steps (b), (c), (d), (e), and (f) refers to the *same* biological activity recited in step (a).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

In this appeal, Appellants request review of the following grounds of rejection set forth in the Final Office Action[1]:

(1) the rejection of pending claims 1-3, 7, 9, 10, 17, 18, 41, 42, and 44 under 35 U.S.C. §102(b) as allegedly being anticipated by British Journal of Cancer 78(2): 189-197, 1998 by Chinol *et al.* (hereafter "Chinol");

(2) the rejection of pending claims 1-3, 7, 9, 10, 17, 18, 41, 42, and 44 under 35 U.S.C. §102(a) as allegedly being anticipated by Int. Journal of Cancer 87:382-390, 2000 by Deckert *et al.* (hereafter "Deckert");

(3) the rejection of pending claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46 under 35 U.S.C. §103(a) as allegedly being unpatentable over Med. Pediatr. Oncol. 34(3):200-205, 2000 by Alvarez *et al.* (hereafter "Alvarez") in view of Bone Marrow Transplant 21(9): 879-885, 1998 by Graham *et al.* (hereafter "Graham"), and Int. J. Hematol. 68(1): 1-18, 1998 by Francis *et al.* (hereafter "Francis");

(4) the rejection of claim 4 under 35 U.S.C. §103(a) as allegedly being unpatentable over Alvarez, Graham, and Francis and further in view of U.S. Patent 6,531,122 to Petersen *et al.* (hereafter "Petersen");

(5) the rejection of claims 8, 11, and 20-22 under 35 U.S.C. §103(a) as allegedly being unpatentable over Alvarez, Graham, and Francis, and further in view of J. Gen. Virol. 72:299-305, 1991 by Roberts *et al.* (hereafter "Roberts"); and

(6) the rejection of claims 18 and 19 under 35 U.S.C. §103(a) as allegedly being unpatentable over Alvarez, Graham, and Francis and further in view of U.S. Patent 4,678,812 to Bollin *et al.* (hereafter "Bollin").

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[1] Appellants acknowledge that, in the Final Office Action the PTO has objected to claim 44 for a minor informality, unrelated to the substantive grounds for rejection. Specifically, the PTO noted that the term "and," which appears at the end of step (e) should be moved to the end of step (f). This objection has no bearing on the reference based rejections set forth in the Office Action. Appellants will correct this informality following receipt of a decision on this appeal.

ARGUMENT

I. The Board Should Reverse the Rejection Under 35 U.S.C. §102 Based Upon Chinol

Claims 1-3, 7, 9, 10, 17, 18, 41, 42 and 44 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated Chinol. Applicant respectfully traverses this rejection.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). See generally MPEP §2131.

A. Claims 1-3, 7, 9, 10, 17, 18, and 41

Here, Chinol fails to disclose "comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent" as recited in claim 1. In this regard, Appellants note that step (a) recites "a biological activity," and that the subsequent references to "the biological activity" refer to the *same* biological activity referenced in step (a).

In contrast to the presently claimed invention, the authors of the Chinol reference used ELISA to determine the titer of antibodies produced against avidin or mPEG modified avidin and used that to determine that modification of avidin with an average of 7 mPEG reduced the immunogenicity of the protein. Despite the availability of a biological assay, namely binding to biotin, they chose to use ELISA to determine titer of antibody produced as a response to repeated injection in order to determine the extent of desired modification. Thus, in contrast to Chinol's use of ELISA, according to the presently claimed invention, the biological activity in circulation (as measured by binding to biotin) could be measured as a guide to determine the extent of modification desired to protect avidin from host mediated inactivation instead of using the titer of antibodies produced in animals as a response to variously modified avidin as a guide to determining the desired extent of modification.

B. Claim 42

With particular regard to claim 42, Chinol fails to disclose "comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that

prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer."

C. Claim 44

With particular regard to claim 44, Appellants note that neither Chinol fails to disclose "(f) comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to determine the relative bioavailability of said first modified therapeutic agent and said second therapeutic agent (g) selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer based upon the comparison of step (f)."

D. Conclusion

For the foregoing reasons, Appellants respectfully request review, reconsideration and reversal of the outstanding rejection under §102 based upon Chinol.

II. The Board Should Reverse the Rejection Under 35 U.S.C. §102 Based Upon Deckert

Claims 1-3, 7, 9, 10, 17, 18, 41, 42 and 44 stand rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Deckert. Appellants respectfully traverse this rejection.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). See generally MPEP §2131.

A. Claims 1-3, 7, 9, 10, 17, 18, and 41

Here, Deckert fails to disclose "comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent" as recited in claim 1. In this regard, Appellants note that step (a) recites "a biological activity" and that the subsequent references to "the biological activity" refer to the *same* biological activity referenced in step (a).

Deckert also fails to disclose assaying a first or second modified therapeutic agent after the first or second modified therapeutic agent "has been administered to a subject." While Deckert used a biological activity, in this case binding affinity of huA33 to A33

antigen on SW1222, to determine the extent of PEGylation or protein modification, Deckert chose the extent of modification that gave less than 50% loss of binding affinity and used a predetermined 30:1 ratio for PEG 5 and 15:1 for PEG 12 and PEG 20 based on acceptable loss of activity and used these ratios for all subsequent experiments. Thus, the extent of PEGylation was determined solely on acceptable loss of biological activity without the use of in vivo studies.

Deckert's work describes a classical immunogenicity study, in which the authors immunized mice four times with unmodified or huA33 modified at a ratio of 30:1 or huA33 modified at a ratio of 15:1 with PEG20. Antibody titer against unmodified and modified huA33 was determined, and they found that animals treated with modified huA33 produced less anti-huA33 antibodies compared to animals treated with unmodified huA33. Two points need to be stressed here. Using two different PEGs, they went into in vivo animal experiments not to determine the extent of modification but rather to find whether the modifications reduced immunogenicity.

Still further, Appellants note that Deckert measured immunogenicity by determining the titer of anti-huA33 antibodies in treated animals. Interestingly, even though the authors had a biological activity that could have been used to determine the serum concentration of huA33, they did not use that method to determine the titer of huA33 in the serum of treated animal after first and subsequent experiments.

B. Claim 42

With particular regard to claim 42, Appellants note that Deckert fails to disclose "comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer."

C. Claim 44

With particular regard to claim 44, Appellants note that Deckert fails to disclose "(f) comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to determine the relative bioavailability of said first modified therapeutic agent and said second

therapeutic agent (g) selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer based upon the comparison of step (f)."

D. Conclusion

For the foregoing reasons, Appellants respectfully request review, reconsideration and reversal of the outstanding rejection under §102 based upon Deckert.

III. The Board Should Reverse the Rejection Under 35 U.S.C. §103 Based Upon the Combination of Alvarez, Graham, and Francis

Claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Alvarez, Graham, and Francis. Appellants respectfully traverse this rejection.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP §2143.03.

A. Claims 1-3, 5-7, 9, 10, 12, 13, 17, 41, and 46

Here, Alvarez, Graham, and Francis taken either individually or in combination, fail to teach or suggest "comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent," as recited in independent claim 1. As discussed above, the references to biological activity in this step relate to the *same* biological activity.

With particular regard to Alvarez, Appellants note that the objective of Alvarez's study was not to determine the extent of modification of asparaginase using various extents of modification with PEG. Further, Alvarez did not assay the biological activity of the agent, in this case asparaginase activity or asparagine level, after the first and subsequent injections in an effort to understand host-mediated inactivation.

Graham adds nothing to resolve Alvarez's deficiencies. Graham used asparaginase modified with one modifying agent with a predetermined extent of modification and method of modification and studied the toxicity of a particular treatment mode. Graham did not report comparison of biological activity of the agent after first and subsequent treatments nor

is the paper concerned with determining whether the agent is adequately protected against host mediated inactivation.

Francis, adds nothing to resolve the deficiencies of the combination of Alvarez and Graham.

If an independent claim is nonobvious under §103, then any claim depending therefrom is nonobvious. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). *See* MPEP 2143.03. Thus, Appellants submit that the claims which ultimately depend from claim 1, are also non-obvious.

B. Claims 42 and 43

With particular regard to claims 42 and 43, Appellants note that none of the cited references, taken either individually or in combination, teaches or suggests "comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer."

C. Claim 44 and 45

With particular regard to claim 44-45, Appellants note that the cited references, individually or together, do not suggest "(f) comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to determine the relative bioavailability of said first modified therapeutic agent and said second therapeutic agent (g) selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer based upon the comparison of step (f)."

D. Conclusion

In view of the foregoing, Appellants respectfully request review, reconsideration and withdrawal of the outstanding rejection under §103 based upon the combination of Alvarez, Graham, and Francis.

IV. The Board Should Reverse the Rejection Under 35 U.S.C. §103 Based Upon the Combination of Alvarez, Graham, Francis, and Petersen

Claim 4 stands rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Alvarez, Graham and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46, and further in view of Petersen. Appellants respectfully traverse this rejection.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP §2143.03.

A. Claim 4

Alvarez, Graham, Francis, and Petersen, taken either individually or in combination, fail to teach or suggest "comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent," as recited in claim 1. As discussed above, the references to biological activity in this step relate to the *same* biological activity referenced in step (a).

With particular regard to Alvarez, Appellants note that the objective of Alvarez's study was not to determine the extent of modification of asparaginase using various extents of modification with PEG. Further, Alvarez did not assay the biological activity of the agent, in this case asparaginase activity or asparagine level, after the first and subsequent injections in an effort to understand host-mediated inactivation.

Graham adds nothing to resolve Alvarez's deficiencies. Graham used asparaginase modified with one modifying agent with a predetermined extent of modification and method of modification and studied the toxicity of a particular treatment mode. Graham did not report comparison of biological activity of the agent after first and subsequent treatments nor is the paper concerned with determining whether the agent is adequately protected against host mediated inactivation.

Francis and Petersen add nothing to resolve the deficiencies of the combination of Alvarez and Graham.

If an independent claim is nonobvious under §103, then any claim depending therefrom is nonobvious. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). *See* MPEP 2143.03. Thus, Appellants submit that claim 4, which ultimately depend from claim 1, is also non-obvious.

B. Conclusion

In view of the foregoing, Appellants respectfully request review, reconsideration and reversal of the outstanding rejection under §103 based upon Alvarez, Graham, Francis, and Petersen.

V. The Board Should Reverse the Rejection Under 35 U.S.C. §103 Based Upon the Combination of Alvarez, Graham, Francis, and Roberts

Claims 8, 11, and 20-22 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Alvarez, Graham, and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13,17, and 41-46, and further in view of Roberts. Appellants respectfully traverse this rejection.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP §2143.03.

A. Claims 8, 11, and 20-22

Alvarez, Graham, Francis, and Roberts, taken either individually or in combination, fail to teach or suggest "comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent," as recited in claim 1. As discussed above, the references to biological activity in this step relate to the *same* biological activity referenced in step (a).

With particular regard to Alvarez, Appellants note that the objective of Alvarez's study was not to determine the extent of modification of asparaginase using various extents of modification with PEG. Further, Alvarez did not assay the biological activity of the agent, in this case asparaginase activity or asparagine level, after the first and subsequent injections in an effort to understand host-mediated inactivation.

Graham adds nothing to resolve Alvarez's deficiencies. Graham used asparaginase modified with one modifying agent with a predetermined extent of modification and method of modification and studied the toxicity of a particular treatment mode. Graham did not report comparison of biological activity of the agent after first and subsequent treatments nor is the paper concerned with determining whether the agent is adequately protected against host mediated inactivation.

Francis and Roberts add nothing to resolve the deficiencies of the combination of Alvarez and Graham.

If an independent claim is nonobvious under §103, then any claim depending therefrom is nonobvious. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). *See* MPEP 2143.03. Thus, Appellants submit that claims 8, 11, and 20-22, which ultimately depend from claim 1, are also non-obvious.

B. Conclusion

In view of the foregoing, Appellants respectfully request review, reconsideration and reversal of the outstanding rejection under §103 based upon Alvarez, Francis, Graham, and Bollin.

VI. The Board Should Reverse the Rejection Under 35 U.S.C. §103 Based Upon the Combination of Alvarez, Graham, Francis, and Bollin

Claims 18 and 19 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Alvarez, Graham, and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46, and further in view of Bollin. Appellants respectfully traverse this rejection.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP §2143.03.

A. Claims 18 and 19

Here, Alvarez, Graham, Francis and Bollin taken either individually or in combination, fail to teach or suggest "comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent," as recited in claim 1. As discussed above, the references to biological activity in this step relate to the same biological activity referenced in step (a).

With particular regard to Alvarez, Appellants note that the objective of Alvarez's study was not to determine the extent of modification of asparaginase using various extents of modification with PEG. Further, Alvarez did not assay the biological activity of the agent, in this case asparaginase activity or asparagine level, after the first and subsequent injections in an effort to understand host-mediated inactivation.

Graham adds nothing to resolve the Alvarez's deficiencies. Alvarez used asparaginase modified with one modifying agent with a predetermined extent of modification and method of modification and studies the toxicity of the a particular treatment mode. Alvarez does not report comparison of biological activity of the agent after first and subsequent treatments nor is the paper concerned with determining whether the agent is adequately protected against host mediated inactivation.

Francis, Petersen, Roberts and Bollin add nothing to resolve the deficiencies of the combination of Alvarez and Graham.

If an independent claim is nonobvious under §103, then any claim depending therefrom is nonobvious. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). *See* MPEP 2143.03. Thus, Appellants submit that claims 18 and 19, which ultimately depend from claim 1, are also non-obvious.

B. Conclusion

In view of the foregoing, Appellants respectfully request review, reconsideration and reversal of the outstanding rejection under §103 based upon Alvarez, Graham, Francis, and Bollin.

CONCLUSION

In summary, the outstanding rejections should be reversed and withdrawn because the Examiner has confused measuring an immune response to the introduction of a biological agent with measuring the extent of remaining functional activity of a biological agent following introduction of that biological agent into a host. As a result, the Examiner has set forth rejections based upon references which do not anticipate or render obvious the presently claimed invention.

Respectfully submitted,

Date 10 November 2006

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CLAIMS APPENDIX

1. A method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer, comprising:

(a) assaying a biological activity of a first modified therapeutic agent after said first modified therapeutic agent has been administered to a subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(b) assaying the biological activity of said first modified therapeutic agent after at least one booster dose of said first modified therapeutic agent has been administered to said subject;

(c) assaying the biological activity of a second modified therapeutic agent after said second modified therapeutic agent has been administered to a subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(d) assaying the biological activity of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said subject; and

(e) comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer.

2. The method of claim 1, wherein said second modified therapeutic agent is modified with the same biocompatible polymer as said first modified therapeutic agent.

3. The method of claim 2, wherein said biocompatible polymer is polyethylene glycol (PEG).

4. The method of claim 3, wherein said PEG is selected from the group consisting of mono-methoxy succinimidyl butanoate (SBA)-PEG, succinimidyl carbonate (SC)-PEG, aldehyde (ALD)-PEG, and succinimidyl propionate (SPA)-PEG.

5. The method of claim 1, wherein said second modified therapeutic agent is modified to the same extent as said first modified therapeutic agent.

6. The method of claim 1, wherein said second modified therapeutic agent and said first modified therapeutic agent are modified with different biocompatible polymers.

7. The method of claim 1, wherein said therapeutic agent comprises a polypeptide.

8. The method of claim 7, wherein said polypeptide is used to treat viral infections in patients in need of treatment thereof.

9. The method of claim 7, wherein said polypeptide is used to treat cancer in patients in need of treatment thereof.

10. The method of claim 7, wherein said polypeptide has a monomeric molecular weight of about 300 daltons to about 300,000 daltons.

11. The method of claim 7, wherein said polypeptide is used to lower glutamine levels in a subject.

12. The method of claim 7, wherein said polypeptide is used to lower asparagine levels in a subject.

13. The method of claim 7, wherein said polypeptide is used to lower asparagine and glutamine levels in a subject.

14. The method of claim 1, wherein said therapeutic agent is a nucleic acid.

15. The method of claim 14, wherein said nucleic acid is used to treat a viral infection in patients in need of treatment thereof.

16. The method of claim 14, wherein said nucleic acid is used to treat cancer in patients in need of treatment thereof.

17. A method of preparing a pharmaceutical composition where host-mediated inactivation is prevented, comprising selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent by the method of claim 1 and modifying said therapeutic agent according to the type of biocompatible polymer, the extent of modification, and the conditions for modification selected.

18. The method of claim 17, wherein said pharmaceutical composition further comprises an excipient.

19. The method of claim 18, wherein said excipient protects said therapeutic agent during lyophilization.

20. The method of claim 17, wherein said therapeutic agent comprises glutaminase-asparaginase.

21. The method of claim 20, wherein said therapeutic agent comprises *Pseudomonas* glutaminase-asparaginase.

22. The method of claim 21, wherein said *Pseudomonas* glutaminase-asparaginase is modified with polyethylene glycol.

23. The pharmaceutical composition prepared by the method of claim 17, wherein said pharmaceutical composition comprises a glutaminase-asparaginase that has been modified with succinimidyl carbonate polyethylene glycol 5000 (SC-PEG 5000), wherein said glutaminase-asparaginase is modified to an extent of from about 21% to about 49% by SC-PEG 5000, and wherein said composition prevents host-mediated inactivation.

24. The composition of claim 23, wherein said glutaminase-asparaginase is modified from about 26% to about 36% by SC-PEG 5000.

25. The composition of claim 24, wherein said glutaminase-asparaginase is modified about 31% by SC-PEG 5000.

26. The pharmaceutical composition prepared by the method of claim 17, wherein said pharmaceutical composition comprises a glutaminase-asparaginase that has been modified with mono-methoxy succinimidyl butanoate polyethylene glycol 5000 (SBA-PEG 5000), wherein said glutaminase-asparaginase is modified from about 25% to about 58% by SBA-PEG 5000, and wherein said composition prevents host-mediated inactivation.

27. The composition of claim 26, wherein said glutaminase-asparaginase is modified from about 30% to about 40% by SBA-PEG 5000.

28. The composition of claim 27, wherein said glutaminase-asparaginase is modified about 35% by SBA-PEG 5000.

29. The pharmaceutical composition prepared by the method of claim 17, wherein said pharmaceutical composition comprises a glutaminase-asparaginase that has been modified with aldehyde polyethylene glycol 2000 (ALD-PEG 2000), wherein said glutaminase-asparaginase is modified from about 45% to about 65% by ALD-PEG 2000, and wherein said composition prevents host-mediated inactivation.

30. The pharmaceutical composition prepared by the method of claim 17, wherein said pharmaceutical composition comprises a glutaminase-asparaginase that has been modified with succinimidyl propionate polyethylene glycol 5000 (SPA-PEG 5000), wherein said modified glutaminase-asparaginase is modified from about 25% to about 65% by SPA-PEG 5000, and wherein said composition prevents host-mediated inactivation.

31. The composition of claim 30, wherein said glutaminase-asparaginase is modified from about 40% to about 55% by SPA-PEG 5000.

32. A composition comprising a glutaminase-asparaginase, wherein said glutaminase-asparaginase has been modified with succinimidyl carbonate polyethylene glycol 5000 (SC-PEG 5000) to an extent of about between 21% and 49%.

33. The modified therapeutic composition of claim 32, wherein said glutaminase-asparaginase has been modified to an extent of about between 26% and 36%.

34. The modified therapeutic composition of claim 33, wherein said glutaminase-asparaginase has been modified to an extent of about 31%.

35. A composition comprising a glutaminase-asparaginase, wherein said glutaminase-asparaginase has been modified with succinimidyl butanoate polyethylene glycol 5000 (SBA-PEG 5000) to an extent of about between 25% and 58%.

36. The modified therapeutic composition of claim 35, wherein said glutaminase-asparaginase has been modified to an extent of about 30% to 40%.

37. The modified therapeutic composition of claim 36, wherein said glutaminase-asparaginase has been modified to an extent of about 35%.

38. A composition comprising a glutaminase-asparaginase, wherein said glutaminase-asparaginase has been modified with aldehyde polyethylene glycol 2000 (ALD-PEG 2000) to an extent of about between 45% and 65%.

39. A composition comprising a glutaminase-asparaginase, wherein said glutaminase-asparaginase has been modified with succinimidyl propionate polyethylene glycol 5000 (SPA-PEG 5000) to an extent of about between 25% and 65%.

40. The modified therapeutic composition of claim 39, wherein said glutaminase-asparaginase has been modified to an extent of about 40% to 55%.

41. The method of claim 1, wherein the subject administered the first modified therapeutic agent is different from the subject administered the second modified therapeutic agent.

42. A method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer, comprising:

(a) selecting a biological activity;

(b) assaying the selected biological activity of step (a) of a first modified therapeutic agent after said first modified therapeutic agent has been administered to a subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(c) assaying the selected biological activity of step (a) of said first modified therapeutic agent after at least one booster dose of said first modified therapeutic agent has been administered to said subject;

(d) assaying the selected biological activity of step (a) of a second modified therapeutic agent after said second modified therapeutic agent has been administered to a subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(e) assaying the selected biological activity of step (a) of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said subject; and

(f) comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer.

43. A method according to claim 42, wherein the step of selecting a biological activity comprises selecting a biological activity other than either antigenicity or immunogenicity.

44. A method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer, comprising:

(a) selecting a biological activity;

(b) assaying the selected biological activity of step (a) of a first modified therapeutic agent after said first modified therapeutic agent has been administered to a subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(c) assaying the selected biological activity of step (a) of said first modified therapeutic agent after at least one booster dose of said first modified therapeutic agent has been administered to said subject;

(d) assaying the selected biological activity of step (a) of a second modified therapeutic agent after said second modified therapeutic agent has been administered to a subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(e) assaying the selected biological activity of step (a) of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said subject; and

(f) comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to determine the relative bioavailability of said first modified therapeutic agent and said second therapeutic agent (g) selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer based upon the comparison of step (f).

45. A method according to claim 44, wherein the step of selecting a biological activity comprises selecting a biological activity other than either antigenicity or immunogenicity.

46. A method according to claim 1, wherein the step of selecting a biological activity comprises selecting a biological activity other than either antigenicity or immunogenicity.

EVIDENCE APPENDIX

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RELATED PROCEEDINGS APPENDIX

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